#### **Claims**

1. A compound of formula I,

wherein

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 $R^1$  represents  $C_{1-12}$  alkyl,  $-(CH_2)_a$ -aryl, or  $-(CH_2)_a$ -Het<sup>1</sup> (all of which are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, halo, cyano, nitro,  $C_{1-4}$  alkyl and/or  $C_{1-4}$  alkoxy);

a represents 0, 1, 2, 3, or 4;

Het<sup>1</sup> represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

X represents O or S;

 $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$  and  $R^{5f}$  independently represent H or  $C_{1-3}$  alkyl;

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substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro,  $C_{1-6}$  alkyl and/or  $C_{1-6}$  alkoxy);

 $R^{15}$  and  $R^{15a}$  independently represent  $C_{1-6}$  alkyl, aryl or  $-(CH_2)_k$ -aryl (all of which are all optionally substituted and/or terminated (as appropriate) by one or more substituents chosen from halo, nitro,  $C_{1-6}$  alkyl and/or  $C_{1-6}$  alkoxy);

c, d, f, h, j and k independently represent 0, 1, 2, 3 or 4;

Het<sup>2</sup> and Het<sup>3</sup> independently represent five to ten-membered heterocyclic rings containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

R<sup>6</sup> represents one or more optional substituents selected from -OH, cyano, halo, amino, nitro, C<sub>1-6</sub> alkyl (optionally terminated by N(H)C(O)OR<sup>20a</sup>), C<sub>1-6</sub> alkoxy, -C(O)N(H)R<sup>21</sup>, -NHC(O)N(H)R<sup>22</sup>, -N(H)S(O)<sub>2</sub>R<sup>23</sup> and/or -OS(O)<sub>2</sub>R<sup>24</sup>;

 $R^{21}$  and  $R^{22}$  independently represent H or  $C_{1-6}$  alkyl;  $R^{20a}$ ,  $R^{23}$  and  $R^{24}$  independently represent  $C_{1-6}$  alkyl;

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A represents a single bond,  $C_{1-6}$  alkylene,  $-N(R^{25})(CH_2)_m$ -,  $-O(CH_2)_m$ - or  $-(CH_2)_mC(H)(OR^{25})(CH_2)_n$ - (in which latter three groups, the  $-(CH_2)_m$ -group is attached to the bispidine nitrogen atom and which latter four groups are optionally substituted by one or more -OH groups);

B represents a single bond,  $C_{1-4}$  alkylene,  $-(CH_2)_pN(R^{26})$ -,  $-(CH_2)_pS(O)_q$ -,  $-(CH_2)_pO$ - (in which three latter groups, the  $-(CH_2)_p$ - group is attached to the carbon atom bearing D and R<sup>4</sup>),  $-C(O)N(R^{26})$ - (in which latter group, the -C(O)- group is attached to the carbon atom bearing D and R<sup>4</sup>),

 $-N(R^{26})C(O)O(CH_2)_p$ - or  $-N(R^{26})(CH_2)_p$ - (in which latter two groups, the  $N(R^{26})$  group is attached to the carbon atom bearing D and  $R^4$ );

m, n and p independently represent 0, 1, 2, 3 or 4;

q represents 0, 1 or 2;

 $R^{25}$  represents H,  $C_{1-6}$  alkyl or  $C(O)R^{27}$ ;

R<sup>26</sup> represents H or C<sub>1-6</sub> alkyl;

 $R^{27}$  represents H,  $C_{1-6}$  alkyl,  $Het^4$  or  $-(CH_2)_r$ -aryl (which latter two groups are optionally substituted and/or terminated (as appropriate) by one or more substituents selected from -OH, cyano, halo, amino, nitro,  $C_{1-6}$  alkyl

10 and/or  $C_{1-6}$  alkoxy);

Het<sup>4</sup> represents a five to ten-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, nitrogen and/or sulfur, and which also optionally includes one or more =O substituents;

r represents 0, 1, 2, 3 or 4;

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or a pharmaceutically acceptable derivative thereof;

provided that:

- (a) R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup>, R<sup>5e</sup> and R<sup>5f</sup> do not all simultaneously represent H;
- 20 (b)  $R^{5a}$  and  $R^{5b}$  do not represent  $C_{1-3}$  alkyl when  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$  and  $R^{5f}$  all represent H; and
  - (c) when D represents -OH or  $-(CH_2)_cN(R^{10})R^{11}$  in which c represents 0, then:-
    - (i) A does not represent  $-N(R^{25})(CH_2)_m$ -,  $-O(CH_2)_m$  or
  - $-(CH_2)_mC(H)(OR^{25})(CH_2)_{n}$  (in which n is 0); and/or
    - (ii) p does not represent 0 when B represents  $-(CH_2)_pN(R^{26})$ -,
    - $-(CH_2)_pS(O)_q$  or  $-(CH_2)_pO$ -.

2. A compound as claimed in Claim 1, wherein R1 represents optionally substituted -(CH<sub>2</sub>)<sub>a</sub>-phenyl, in which a is 0, 1, 2 or 3, or optionally substituted, optionally unsaturated, linear, branched or cyclic, C<sub>1-8</sub> alkyl (which latter group may also be interrupted by an oxygen atom).

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- 3. A compound as claimed in Claim 1 or Claim 2, wherein R<sup>2</sup> represents H.
- 4. A compound as claimed in any one of the preceding claims, wherein R<sup>3</sup> represents H. 10
  - 5. A compound as claimed in any one of the preceding claims, wherein R<sup>4</sup> represents H or  $C_{1-3}$  alkyl.
- 6. A compound as claimed in any one of the preceding claims, wherein R5a 15 and R5b either both represent H or both represent methyl.
  - 7. A compound as claimed in any one of the preceding claims, wherein  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$  and  $R^{5f}$  independently represent H or  $C_{1-2}$  alkyl.

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8. A compound as claimed in any one of the preceding claims, wherein R<sup>6</sup> represents one or more substituents selected from C<sub>1-6</sub> alkyl (which alkyl group is optionally terminated by a N(H)C(O)OR<sup>20a</sup> group (in which R<sup>20a</sup> represents C<sub>1-5</sub> alkyl)), cyano, nitro, amino, C(O)N(H)R<sup>21</sup> and/or

 $-N(H)S(O)_2R^{23}$ . 25

> 9. A compound as claimed in any one of the preceding claims, wherein X represents O.

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- 10. A compound as claimed in any one of the preceding claims, wherein A represents a single bond or linear, or branched, C<sub>1-4</sub> alkylene (which group is also optionally interrupted by O).
- 11. A compound as claimed in any one of the preceding claims, wherein B represents a single bond, C<sub>1-4</sub> alkylene, -(CH<sub>2</sub>)<sub>p</sub>O- or -(CH<sub>2</sub>)<sub>p</sub>N(R<sup>26</sup>)- (in which latter two cases p is 1, 2 or 3).
- 12. A compound as claimed in any one of the preceding claims, wherein D represents H, OR<sup>9</sup> (in which R<sup>9</sup> represents H, C<sub>1-3</sub> alkyl or optionally substituted phenyl) or N(H)R<sup>10</sup> (in which R<sup>10</sup> represents H or C<sub>1-4</sub> alkyl).
  - 13. A pharmaceutical formulation including a compound as defined in any one of Claims 1 to 12 in admixture with a pharmaceutically-acceptable adjuvant, diluent or carrier.
    - 14. A pharmaceutical formulation for use in the prophylaxis or the treatment of an arrhythmia, comprising a compound as defined in any one of Claims 1 to 12.

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- 15. A compound as defined in any one of Claims 1 to 12 for use as a pharmaceutical.
- 16. A compound as defined in any one of Claims 1 to 12 for use in the prophylaxis or the treatment of an arrhythmia.
  - 17. The use of a compound as defined in any of one Claims 1 to 12 as active ingredient in the manufacture of a medicament for use in the prophylaxis or the treatment of an arrhythmia.

- 18. The use as claimed in Claim 17, wherein the arrhythmia is an atrial or a ventricular arrhythmia.
- 19. A method of prophylaxis or treatment of an arrhythmia which method comprises administration of a therapeutically effective amount of a compound as defined in any one of Claims 1 to 12 to a person suffering from, or susceptible to, such a condition.
- 20. A process for the preparation of a compound of formula I as defined in Claim 1 which comprises:
  - (a) reaction of a compound of formula II,

wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup>, R<sup>5e</sup>, R<sup>5f</sup>, R<sup>6</sup>, A, B and D are as defined in Claim 1 with a compound of formula III,

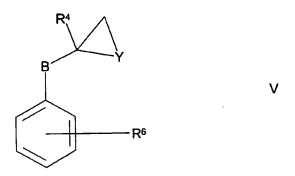
$$R^{1}XC(O)L^{1}$$

wherein  $L^1$  represents a leaving group and  $R^1$  and X are as defined in Claim 1;

(b) for compounds of formula I in which A represents  $CH_2$  and D represents -OH or  $-N(H)R^{10}$ , wherein  $R^{10}$  is as defined in Claim 1, reaction of a compound of formula IV,

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wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$ ,  $R^{5f}$  and X are as defined in Claim 1, with a compound of formula V,

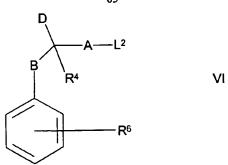


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wherein Y represents O or  $N(R^{10})$  and  $R^4$ ,  $R^6$ ,  $R^{10}$  and B are as defined in Claim 1;

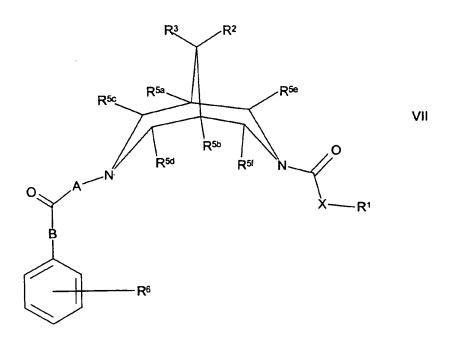
(c) reaction of a compound of formula IV, as defined above, with a compound of formula VI,

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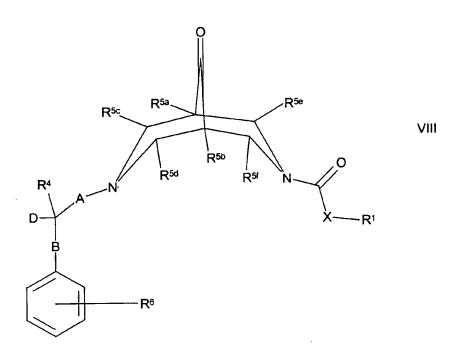


wherein  $L^2$  represents a leaving group and  $R^4$ ,  $R^6$ , A, B and D are as defined in Claim 1;

5 (d) for compounds of formula I in which D represents H or OH and R<sup>4</sup> represents H, reduction of a compound of formula VII,



- wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5c}$ ,  $R^{5c}$ ,  $R^{5f}$ ,  $R^6$ , A, B and X are as defined in Claim 1;
  - (e) for compounds of formula I in which one of R<sup>2</sup> and R<sup>3</sup> represents H or OH and the other represents H, reduction of a corresponding compound of formula VIII,



wherein  $R^1$ ,  $R^4$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5c}$ ,  $R^{5c}$ ,  $R^{5c}$ ,  $R^{5f}$ ,  $R^6$ , A, B, D and X are as defined in Claim 1;

(f) for compounds of formula I in which  $R^2$  and/or  $R^3$  represent  $OC(O)R^8$  and  $R^8$  is as defined in Claim 1, coupling of a corresponding compound of formula I in which  $R^2$  and/or  $R^3$  (as appropriate) represent OH and a compound of formula VIIIA,

R<sup>8</sup>CO<sub>2</sub>H VIIIA

wherein R<sup>8</sup> is as defined in Claim 1;

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(g) for compounds of formula I in which D represents  $-(CH_2)_cNH_2$ , reduction of a corresponding compound of formula IX,

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wherein c,  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$ ,  $R^{5f}$ ,  $R^6$ , A, B and X are as defined in Claim 1;

(h) for compounds of formula I in which D represents  $-N(R^{11})C(O)NH(R^{17})$ , in which  $R^{11}$  and  $R^{17}$  are as defined in Claim 1, except that  $R^{11}$  does not represent  $C(O)R^{20}$ , reaction of a corresponding compound of formula I in which D represents  $-N(R^{11})H$ , in which  $R^{11}$  is as defined in Claim 1 except that is does not represent  $C(O)R^{20}$  in which  $R^{20}$  is as defined in Claim 1, with a compound of formula X,

 $R^{17}N = C = O X$ 

wherein R<sup>17</sup> is as defined in Claim 1;

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- (i) for compounds of formula I in which D represents -N(H)[C(O)]<sub>2</sub>NH<sub>2</sub>, reaction of a corresponding compound of formula I in which D represents -NH<sub>2</sub> with oxalic acid diamide;
- (j) for compounds of formula I in which D represents -N(R<sup>11</sup>)C(O)R<sup>18</sup>, in which R<sup>11</sup> and R<sup>18</sup> are as defined in Claim 1, except that R<sup>11</sup> does not represent C(O)R<sup>20</sup>, reaction of a corresponding compound of formula I in which D represents -N(R<sup>11</sup>)H, in which R<sup>11</sup> is as defined in Claim 1 except that it does not represent C(O)R<sup>20</sup>, with a compound of formula XI,

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 $R^{18}C(O)R^{x}$ 

XI

wherein R<sup>x</sup> represents a suitable leaving group and R<sup>18</sup> is as defined in Claim 1;

(k) for compounds of formula I in which D represents -N(H)R<sup>10</sup> and R<sup>10</sup> is as defined in Claim 1 except that it does not represent H or -C(NH)NH<sub>2</sub>, reaction of a corresponding compound of formula I wherein D represents - NH<sub>2</sub> with a compound of formula XIA,

 $R^{10a}L^1$ 

XIA

wherein  $R^{10a}$  represents  $R^{10}$  as defined in Claim 1, except that it does not represent H or  $-C(NH)NH_2$  and  $L^1$  is as defined above;

- (l) for compounds of formula I which are bispidine-nitrogen N-oxide derivatives, oxidation of the corresponding bispidine nitrogen of a corresponding compound of formula I;
- (m) for compounds of formula I which are  $C_{1-4}$  alkyl quaternary ammonium salt derivatives, in which the alkyl group is attached to a bispidine nitrogen, reaction, at the bispidine nitrogen, of a corresponding compound of formula I with a compound of formula XII,

RªHal

XII

wherein R<sup>a</sup> represents C<sub>1.4</sub> alkyl and Hal represents Cl, Br or I;

(n) for compounds of formula I in which D and  $R^4$  both represent H, A represents  $C_{1-6}$  alkylene, B represents  $-N(R^{26})(CH_2)_{p^-}$  and  $R^{26}$  and p are as defined in Claim 1, reaction of a compound of formula XIII,

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$$R^{5c}$$
 $R^{5a}$ 
 $R^{5b}$ 
 $R^{5b}$ 

wherein  $A^a$  represents  $C_{1-6}$  alkylene and  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^{5a}$ ,  $R^{5b}$ ,  $R^{5c}$ ,  $R^{5d}$ ,  $R^{5e}$ ,  $R^{5f}$ ,  $R^{26}$  and X are as defined in Claim 1 with a compound of formula XIV,

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(CH<sub>2</sub>)<sub>p</sub>Hal XIV

wherein R<sup>6</sup> and p are as defined in Claim 1 and Hal is defined above;

(o) reaction of a compound of formula II, as defined above, with a compound of formula XV,

R<sup>1</sup>XH XV

wherein R<sup>1</sup> and X are as defined in Claim 1, in the presence of 1,1'-carbonyldiimidazole;

(p) for compounds of formula I in which  $R^9$  represents optionally substituted  $C_{1-6}$  alkyl, optionally substituted - $(CH_2)_d$ -aryl or optionally substituted - $(CH_2)_d$ -Het², reaction of a corresponding compound of formula I, in which D represents OH with a compound of formula XVI,

R<sup>∞</sup>OH XVI

wherein  $R^{9a}$  represents optionally substituted  $C_{1-6}$  alkyl, optionally substituted - $(CH_2)_d$ -aryl or optionally substituted - $(CH_2)_d$ -Het<sup>2</sup>, and d and Het<sup>2</sup> are as defined in Claim 1;

(q) for compounds of formula I in which  $R^9$  represents optionally substituted  $C_{1-6}$  alkyl, optionally substituted - $(CH_2)_d$ -aryl or optionally substituted - $(CH_2)_d$ -Het<sup>2</sup>, reaction of a compound of formula XVII,

$$R^{5c}$$
 $R^{5a}$ 
 $R^{5e}$ 
 $R^{5e}$ 

wherein L<sup>2</sup> is as defined above and R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup>, R<sup>5e</sup>, R<sup>5f</sup>, R<sup>6</sup>, X, A and B are as defined in Claim 1 with a compound of formula XVI as defined above;

(r) for compounds of formula I in which  $R^9$  represents  $C(O)R^{12}$  and  $R^{12}$  is as defined in Claim 1, reaction of a corresponding compound of formula I in which D represents OH with a compound of formula XVIII,

R<sup>12</sup>CO<sub>2</sub>H XVIII

wherein R<sup>12</sup> is as defined in Claim 1;

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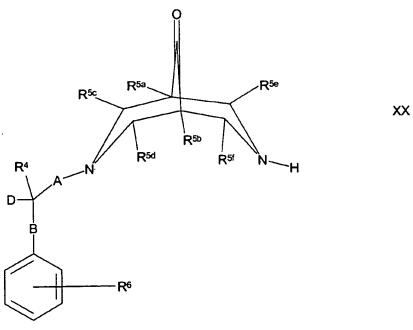
(s) for compounds of formula I in which one or both of  $R^2$  and  $R^3$  represent  $-N(R^{7a})R^{7b}$  in which one or both of  $R^{7a}$  and  $R^{7b}$  represents  $C_{1-6}$  alkyl, alkylation of a corresponding compound of formula I in which  $R^2$ 

and/or  $R^3$  represent  $-N(R^{7a})R^{7b}$  (as appropriate) in which  $R^{7a}$  and/or  $R^{7b}$  (as appropriate) represent H, using a compound of formula XVIIIA,

 $R^{7c}L^1$  XVIIIA

wherein  $R^{7c}$  represents  $C_{1-6}$  alkyl and  $L^1$  is as defined above;

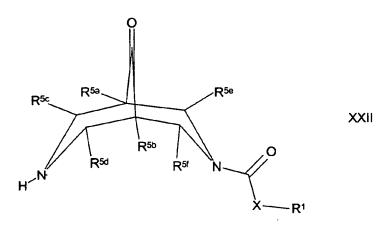
- 5 (t) conversion of one R<sup>6</sup> substituent to another; or
  - (u) deprotection of a protected derivative of a compound of formula I as defined in Claim 1.
- 21. A compound of formula II as defined in Claim 20, or a protected derivative thereof.
  - 22. A compound of formula IV as defined in Claim 20, or a protected derivative thereof.
- 23. A compound of formula VIII as defined in Claim 20, or a protected derivative thereof.
  - 24. A compound of formula XX,



wherein R<sup>4</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup>, R<sup>5e</sup>, R<sup>5f</sup>, R<sup>6</sup>, A, B and D are as defined in Claim 1, or a protected derivative thereof.

## 25. A compound of formula XXII,

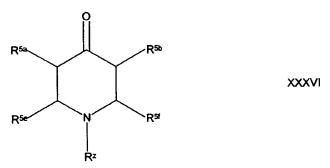
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wherein R<sup>1</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5c</sup>, R<sup>5d</sup>, R<sup>5e</sup>, R<sup>5f</sup> and X are as defined in Claim 1, or a protected derivative thereof.

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26. A process for the preparation of a compound of formula VIII, XX, XXII or XXXV (as defined herein, in which, in all cases,  $R^{5c}$  and  $R^{5d}$  both represent H), which comprises reaction of a compound of formula XXXVI,



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wherein R<sup>z</sup> represents H or -C(O)XR<sup>1</sup> and R<sup>1</sup>, R<sup>5a</sup>, R<sup>5b</sup>, R<sup>5e</sup>, R<sup>5f</sup> and X are as defined in Claim 1, or a protected derivative thereof, with (as appropriate) either:

(1) a compound of formula XXXVII,

or a protected derivative thereof, wherein R4, R6, A, B and D are as defined

- 5 in Claim 1; or
  - (2) NH<sub>3</sub> (or a protected derivative thereof), in all cases in the presence of a formaldehyde.

International application No.

#### PCT/SE 00/01252 A. CLASSIFICATION OF SUBJECT MATTER IPC7: C07D 471/08, C07D 471/20, A61K 31/435 According to International Patent Classification (IPC) or to both national classification and IPC **B. FIELDS SEARCHED** Minimum documentation searched (classification system followed by classification symbols) IPC7: C07D, A61K Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched SE,DK,FI,NO classes as above Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) C. DOCUMENTS CONSIDERED TO BE RELEVANT Relevant to claim No. Citation of document, with indication, where appropriate, of the relevant passages Category\* X EP 0308843 A2 (BASF AKATIENGESELLSCHAFT), 1-20,21,24 29 March 1989 (29.03.89) 22,23,25,26 A EP 0306871 A2 (KALI-CHEMIE PHARMA GMBH), 1-26 A 15 March 1989 (15.03.89) WO 9107405 A1 (THE BOARD OF REGENTS OF OKLAHOMA 1-26 A STATE UNIVERSITY), 30 May 1991 (30.05.91) 1-26 US 5786481 A (KENNETH DARRELL BERLIN ET AL), A 28 July 1998 (28.07.98) See patent family annex. χl Further documents are listed in the continuation of Box C. later document published after the international filing date or priority date end not in conflict with the application but cited to understand Special categories of cited documents: "A" document defining the general state of the art which is not considered the principle or theory underlying the invention to be of particular relevance "X" document of particular relevance: the claimed invention cannot be "E" erlier document but published on or after the international filing date considered novel or cannot be considered to involve an inventive step when the document is taken alone document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art special reason (as specified) document referring to an oral disclosure, use, exhibition or other document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 26 -10- 2000 19 October 2000 Name and mailing address of the ISA/ Authorized officer Sw dish Patent Office

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International application No.
PCT/SE 00/01252

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			Polaron and delivery
Category*	Gtation of document, with indication, where appropriate, of the rele	evant passages	Relevant to claim No
P,A	WO 9931100 A1 (ASTRA AKTIEBOLAG), 24 June 199 (24.06.99)	99	1-26
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Form PCT/ISA/210 (continuation of second sheet) (July 1992)

International application No. PCT/SE00/01252

Вох	ιI	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)					
This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:							
1.	$\boxtimes$	Claims Nos.: 19 because they relate to subject matter not required to be searched by this Authority, namely:					
		See PCT Rule 39.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.					
2.		Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:					
3.		Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).:					
Bo	хIJ	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)					
		mational Searching Authority found multiple inventions in this international application, as follows:					
1.		As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.					
2.	Ш	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.					
3.		As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:					
4.		No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:					
Re	Remark on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.						

Information on patent family members

International application No.
PCT/SE 00/01252

Patent document cited in search report			Publication date	Patent family member(s)		Publication date	
EP	0308843	A2	29/03/89	SE	0308843 T3	<del></del>	
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